

# Multi-Gene Hereditary Cancer Testing among Men with Breast Cancer

Krystal Brown, PhD<sup>1</sup>; Gregory Callip, PharmD, MPH, PhD<sup>2</sup>; Ryan Bernhisel, MStat<sup>1</sup>; Brent Evans, MS<sup>1</sup>; Eric Rosenthal, PhD, ScM<sup>1</sup>; Jennifer Saam, PhD<sup>1</sup>; Johnathan Lancaster, MD, PhD<sup>1</sup>; Kent Hoskins, MD<sup>2</sup>

1. Myriad Genetic Laboratories, Inc., Salt Lake City, Utah    2. University of Illinois at Chicago, Chicago, Illinois

## BACKGROUND

- All men with a personal diagnosis of breast cancer are candidates for *BRCA1* and *BRCA2* genetic testing because pathogenic variants in these genes have a known association with breast cancer risk in both men and women.<sup>1</sup>
- Additional genes with known breast cancer risk in women are now routinely included in multi-gene panel testing.
- Here, we evaluated the outcomes of multi-gene panel testing in a large cohort of men with breast cancer.

## METHODS

### COHORT

- This analysis includes 1,534 men with breast cancer who had testing with a multi-gene pan-cancer panel between September 2013 and April 2017.

### GENETIC TESTING

- The multi-gene panel included *BRCA1*, *BRCA2*, *ATM*, *CHEK2*, *PALB2*, *NBN*, *BARD1*, *PTEN*, *BRIP1*, *RAD51C*, *RAD51D*, *MLH1*, *MSH2*, *EPCAM*, *MSH6*, *PMS2*, *APC*, *MUTYH*, *POLD1*, *POLE*, *GREM1*, *BMPR1A*, *SMAD4*, *TP53*, *STK11*, *CDH1*, *CDKN2A*, and *CDK4*.
- All genes on the panel were available for the full time period except for *POLD1*, *POLE*, and *GREM1*, which were included starting in July 2016.
- Sequence and large rearrangement analysis was performed for all genes except for *POLD1*, *POLE* (sequencing only) and *EPCAM*, *GREM1* (large rearrangement only).
- Pathogenic variants (PVs) are those that received a laboratory classification of Deleterious or Suspected Deleterious.

### ANALYSIS

- Clinical information was obtained from provider-completed test request forms.
- Personal cancer history and family cancer history were compared for men with PVs in *BRCA1* or *BRCA2* and men with PVs in other genes associated with breast cancer.
- The clinical presentation of men with PVs in genes with no known association with breast cancer was assessed separately.

## RESULTS

- 231 (15.1%) men with breast cancer were found to carry one or more PVs (Table 1).
  - PVs in *BRCA2* (10.0%) and *CHEK2* (2.0%) were most common.
  - 7 men had a PV in two different genes, most commonly *BRCA1/2* and *CHEK2* (n=5).

Table 1. Distribution of PVs in Men with Breast Cancer

Gene	Total PVs N (%)	Prevalence	Second Breast Cancer
<b>BRCA1 &amp; BRCA2</b>			
<i>BRCA2</i>	153 (66.2%)	10.0%	3
<i>BRCA1</i>	10 (4.3%)	0.7%	1 <sup>†</sup>
Sub-total	162 (70.1%)*	10.6%	4
<b>Other Breast Cancer-Risk Genes</b>			
<i>CHEK2</i> **	30 (13.0%)	2.0%	2
<i>ATM</i>	14 (6.1%)	0.9%	2 <sup>†</sup>
<i>PALB2</i>	14 (6.1%)	0.9%	0
<i>NBN</i>	5 (2.2%)	0.3%	0
<i>BARD1</i>	4 (1.7%)	0.3%	1
<i>CDH1</i>	1 (0.4%)	<0.1%	1
<i>TP53</i>	1 (0.4%)	<0.1%	0
Sub-total	69 (29.9%)	4.5%	6
<b>Lynch Syndrome Genes</b>			
<i>MSH6</i>	2 (0.9%)	0.1%	0
<i>MLH1</i>	1 (0.4%)	<0.1%	0
<i>PMS2</i>	1 (0.4%)	<0.1%	0
Sub-total	4 (1.7%)	0.3%	0
<b>Other Cancer-Risk Genes</b>			
<i>BRIP1</i>	1 (0.4%)	<0.1%	0
<i>CDKN2A</i>	1 (0.4%)	<0.1%	0
Sub-total	2 (0.9%)	0.1%	0
<b>Total</b>	<b>231*</b>	<b>15.1%</b>	<b>9 (3.9%)<sup>†</sup></b>

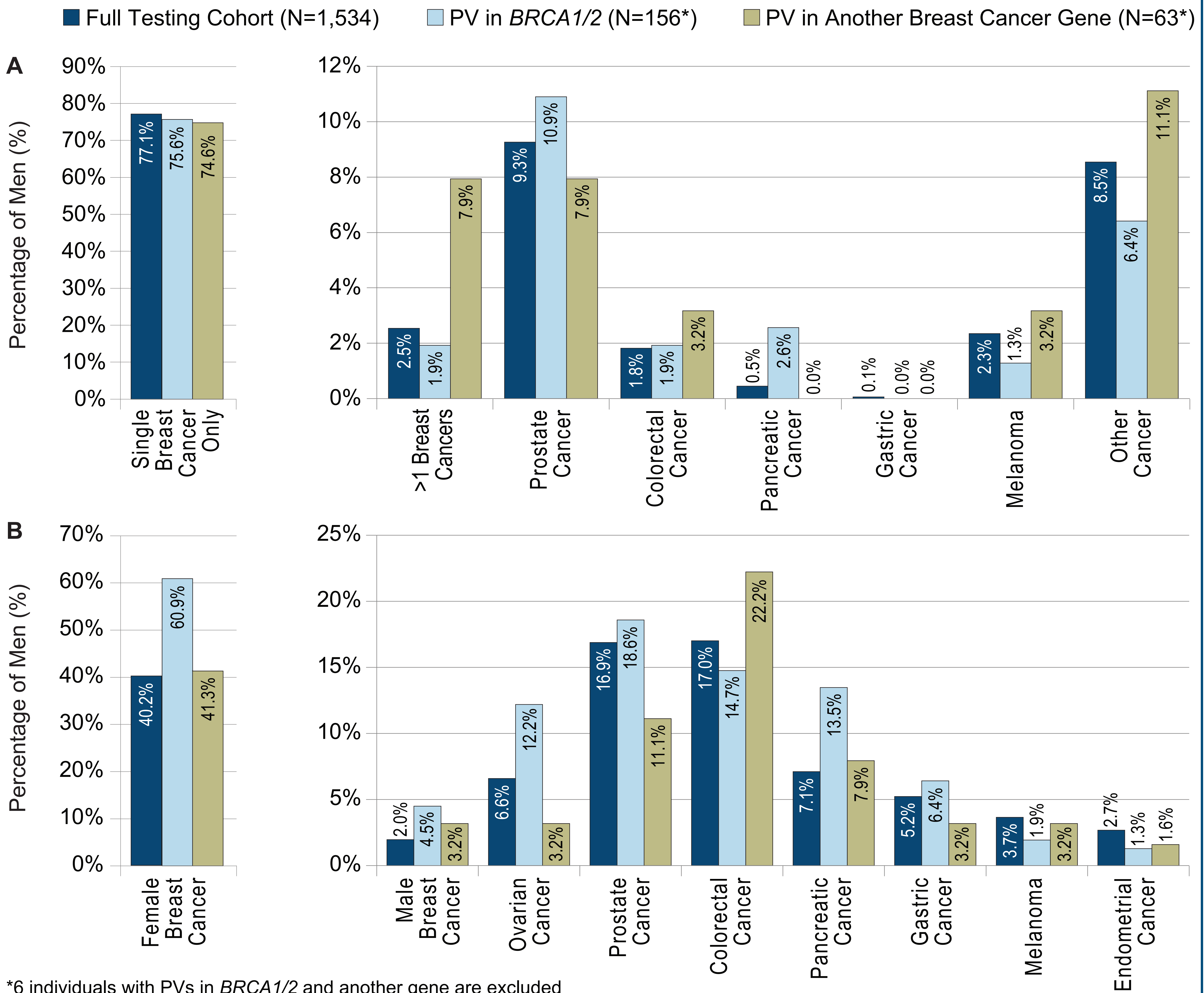
\*7 men had PVs in two different genes (*BRCA2* and *CHEK2*, 4; *BRCA1* and *CHEK2*, 1; *BRCA1* and *ATM*, 1; *BRCA1* and *BRCA2*, 1)

\*\*23/30 (76.7%) PVs in *CHEK2* were c.1100del

<sup>†</sup>1 man with PVs in both *BRCA1* and *ATM* had a second breast cancer

- There were no substantial differences in the median age-at-diagnosis for men without a PV (66) compared to those with a PV in *BRCA1/2* (66) or a PV in another gene (63).
- Fewer men with a PV in *BRCA1/2* had a second breast cancer relative to men with a PV in another breast cancer risk gene (1.9% versus 7.9%; Figure 1).
- A personal and/or family history of prostate, pancreatic, female breast, and ovarian cancer was more common among men with a PV in *BRCA1/2* compared to men with a PV in another breast cancer risk gene (Figure 1).
  - This is consistent with the penetrance and cancer spectrum of *BRCA1/2* relative to the other breast cancer genes.

Figure 1. (A) Personal and (B) Family Cancer History (First and Second Degree Relatives)



- A personal and family history of colon cancer was reported for only one individual with a mutation in a gene associated with Lynch syndrome (Table 2).
- One man with a PV in *MSH6* was diagnosed with breast cancer at age 39 and reported no other personal or family cancer history (Table 2).

Table 2. Personal and Family Cancer History for Men with PVs in Genes with No Known Breast Cancer Risk

Gene	Personal History (Age at Dx)	Family History (Age at Dx)
<i>MLH1</i>	Breast (65) Colon (36) Duodenum (61) Melanoma (62)	FDR: Colon (23, 43, 48) and Ovarian (46); FDR: Colon (75); FDR: Rectum (62)
<i>MSH6</i>	Breast (62) Other (75)	FDR: Breast (63); SDR: Gastric (70); SDR: Pancreas (70)
<i>MSH6</i>	Breast (39)	None
<i>PMS2</i>	Breast (79)	None
<i>BRIP1</i>	Breast (65)	FDR: Colon (67)
<i>CDKN2A</i>	Breast (70)	FDR: Breast (age unknown); SDR: Breast (age unknown)

Dx, Diagnosis; FDR, First degree relative; SDR, Second degree relative

## CONCLUSIONS

- Nearly one third of all PVs identified in men with breast cancer here were in a gene other than *BRCA1* or *BRCA2*.
- PVs were identified in several genes with no known breast cancer risk, very few of which were predicted by additional personal and family cancer history.
- There were no obvious differences in the clinical presentation of men with PVs in *BRCA1* or *BRCA2* compared to men with PVs in most of the other panel genes, which suggests that multi-gene panel testing may be appropriate for all men with breast cancer regardless of other personal or family history.

## REFERENCES

- Daly M, Pilarski R, Berry M, et al. Genetic/Familial High-Risk Assessment: Breast and Ovarian. NCCN Clinical Practice Guidelines in Oncology. Version 2.2017.